UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/719,336	03/22/2001	Mangus Von Knebel-Doeberitz	4121-121	7154

7590 07/02/2002

Steven J Hultquist
P O Box 14329
Research Triangle Park, NC 27709

EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	10

DATE MAILED: 07/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application N .	Applicant(s)	
	09/719,336	VON KNEBEL-DOEBERITZ ET AL.	
	Examiner	Art Unit	
	Celine Qian	1636	

-- The MAILING DATE of this communicati n appears on th cover sheet with the c rrespondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-12 are pending in the application.

This Office Action is in response to the Amendment filed on 4/17/02.

Drawings

The drawings are objected to because of the informalities as indicated by Draftsperson on PTO form 948 (see attached form). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance. Any response to this office action which does not response to the above objections will be considered non-responsive.

Response to Amendment

The objection to the specification has been withdrawn in light of Applicants' amendment.

The rejection of claims 1-6 under 35 U.S.C. 112 second paragraph (use claims) has been withdrawn in light of Applicants' amendment of the claims.

Claims 1-9 and newly added claims 10-12 stand rejected under 35 U.S.C. 112 first paragraph for reasons made of record in the Office Action mailed on 1/17/02 and further discussed below.

Claims 1-6 and 10-12 are rejected under 35 U.S.C. 112, second paragraph as necessitated by Applicants amendment of claims for reasons discussed below.

Response to Arguments

In response to the rejection of claims 1-9 under 35 U.S.C. 112 first paragraph, Applicants argue that the specification has provided sufficient support with regard to the dosage and route of administration of AAV2 virus for practicing the method as claimed. Applicants further argue

that the in vitro data and in vivo data in murine model provided in examples 1-3 is predictive of human efficacy for cancer treatment. Applicants cited 5 references to demonstrate that mouse model is an effective and acceptable animal model wherein effective results in animal testing can be extrapolated to human efficacy. In addition, Applicants argue that FDA approval is not a prerequisite for finding a compound useful within the meaning of patent law, therefore, no clinical studies need to be carried out.

Applicants' arguments and the references introduced have been fully considered but they are not persuasive. The state of art at the time of filing teaches that anti-tumor drugs in xenograft murine models is not predictive of their efficacy. Gura (1997, Science, Vol. 278 : 1041-1042) states that not only very few drugs that showed anti-tumor activity in xenografts made it to clinic, but that the xenograft models also miss effective drugs according to a study conducted by NCI (see page 1041, 1st col., 3rd paragraph). In the instant application (example 3), Applicants implanted human small cell lung cancer cells into nude mice. The nude mice are immuno-deficient, thus cannot reject the foreign tissues and resulted in unchecked tumor growth. As the Gura article points out the xenograft mouse model with implanted human tumor does not or rather cannot react to the drugs exactly as the human body does. This is vastly different from tumor growth in a human body where the immune system is functional.

Sausville, associate director of cancer treatment and diagnosis for the developmental therapeutics program at the NCI, also states that the compounds that are good mouse drugs are not necessarily good human drugs (see page 1041, 2nd col., 3rd paragraph, last sentence). Therefore, the specification needs to provide guidance to overcome the unpredictability as discussed above so that one skilled in the art would not have to engage in undue experimentation

discussed above so that one skilled in the art would not have to engage in undue experimentation to practice the method of lowering chemotherapy induced resistance in a patient by administering AAV-2. However, as discussed previously in the Office Action mailed 1/17/02 and above, the specification fails to provide such guidance.

The specification only discloses that AAV-2 sensitizes a number of small cell lung cancer cell lines to chemotherapeutic agents etopside and cisplatin. However, this does not provide sufficient information for whether AAV-2 would achieve same effect in humans; because cell culture study does not provide information about whether AAV-2 will make it to the tumor sites in sufficient amount to achieve the same effect in vivo. Although the specification discloses that co-administration of AAV-2 with chemotherapeutic agents to xenografted mouse model stop and reverse tumor growth in otherwise chemo-resistant tumor, whether it will stop and reverse tumor growth in a cancer patient is unpredictable due to the different environment the tumor resides. In addition, the route of administering AAV-2 to human cancer patients also adds unpredictability for practicing said method. In the xenograft model as disclosed in the specification, the AAV-2 is administered either directly to the tumor site or intraperitoneally, and whether other routes of administration such as oral, subcutaneous or intravenous administration would achieve same effect is unpredictable.

Applicant cited case law *Scott v. Finney, In re Marzocchi, In re Brana* and *In re Jolla* to show that the standard for enablement is not same as that drug marketing approval by the FDA so that clinical study is not required. This argument is neither persuasive nor on point with the rejection made of record which established a prima facie case of non-enablement based on the highly unpredictable nature of the claimed invention and the apparent lack of teachings/guidance

from the present specification that is commensurate in scope with the broadly claimed invention. Contrary to Applicants' implied assertions, the standard applied in the rejection of record are those set forth for 35 U.S.C. 112, first paragraph, enablement. As such, one of skilled in the art would have to engage in undue amount of experimentation to overcome the art recognized unpredictability to practice the method as claimed.

New Grounds of Rejection Necessitated by Applicants' Amendment

Claims 10-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons made of record in the Office Action mailed on 1/17/02 and as discussed above.

The claimed invention is a method of reversing chemotherapy-induced resistance in patient suffering from a small cell lung cancer by administering AAV2 with a chemotherapeutic agent to said patient. The claimed invention has same method steps as the method claimed in claims 1-6. Therefore, the invention is considered not enabled for reasons made of record in the Office Action mailed on 1/17/02 and discussed above.

Claims 1-6 and 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 and 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps.

See MPEP § 2172.01. The omitted steps are: The step that determines whether chemotherapy-induced resistance is lowered/reversed is not recited in the claims.

Claim 5 recites the limitation "use" in line 1. There is insufficient antecedent basis for this limitation in the claim because neither claims 1 to 4 recites this limitation.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
July 1, 2002

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600